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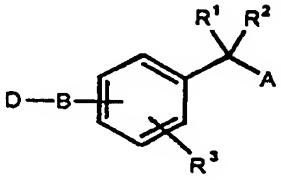

(I)

(57) Abstract

The present invention relates to compounds of general formula (I) as cyclooxygenase–I selective inhibitors, to the pharmaceutically acceptable salts and solvates thereof, and to pharmaceutical compositions containing them. The compounds show an analgesic and antiinflammatory action, while, in patients with pre–existent ulcers and gastrointestinal disturbances, they do not cause any higher incidence of these conditions nor worsen them neither delay the healing thereof. The present invention also relates to a process for the preparation of the compounds as well as to the therapeutic use thereof.

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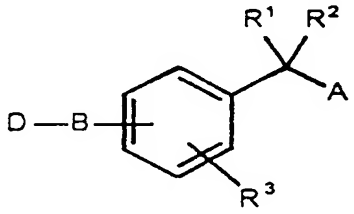
CYCLOOXYGENASE-I SELECTIVE INHIBITORS AND THE USE THEREOF AS ANALGESIC, ANTIINFLAMMATORY AND ANTIARTHRITIC AGENTS.

SUMMARY OF THE INVENTION

The present invention relates to compounds of general formula I,



I

as cyclooxygenase-I selective inhibitors, to the pharmaceutically acceptable salts and solvates thereof, and to pharmaceutical compositions containing them. The compounds show an analgesic and antiinflammatory action, while, in patients with ulcers and pre-existent gastrointestinal disturbances, they neither cause any higher incidence of these conditions nor worsen them or delay the healing thereof. The present invention also relates to a process for the preparation of the compounds as well as to the therapeutic use thereof.

TECHNOLOGICAL BACKGROUND

It is well known that most eicosanoids, prostaglandins, leukotrienes and related compounds derive from a fatty acid having 20 carbons and 4 unsaturations, called arachidonic acid (AA), which fundamentally esterifies the hydroxyl at the 2- position of the glycerol of the phospholipids contained in the cell membranes. AA is released from the phospholipid

containing it by the action of a lipase, phospholipase A_2 (PLA_2) ("CRC Handbook of Eicosanoids and Related Lipids", vol. II, Ed. A.L.Willis, CRS Press Inc., Florida (1989)). After being released AA is metabolized in mammals mainly by two different pathways or enzyme systems. Through lipoxygenase it produces leukotrienes, the most important being LTB_4, and the peptide-leukotrienes LTC_4, LTD_4 and LTE_4. All of them are also involved in inflammatory reactions (Bailey and Casey, Ann. Rep. Med.Chem., 17, 203 (1982)). Through cyclooxygenase, prostaglandins and thromboxanes are produced, the most significant being PGE_2 and TxA_2. Prostaglandins are directly involved in gastrointestinal mucosa function, renal function and the like and also as mediators of both acute and chronic inflammation. Conventional non steroidal antiinflammatory compounds (NSAIDs) act inhibiting cyclooxygenase and, therefore, interrupting the formation of prostaglandins both in normal and in inflamed tissues (J.R. Vane, Nature, 231, 232-235 (1971)).

The presence of two cyclooxygenase isoenzymes, cyclooxygenase-I (COX-I) and cyclooxygenase-II (COX-II) has recently been described (W. Xie, et al. Proc. Nat. Acad. Sci. USA, 88, 2692-2696 (1991)). The isoenzyme I is present in most tissues, whereas COX-II is induced in response to a variety of agents, such as endotoxins, cytokines, mitogens, etc. Furthermore, whereas COX-I is related with the modulation action of prostaglandins on the gastric mucosa and the renal functions, COX-II seems to be related with the function of these compounds as mediators in the inflammatory response (W. Xie, et al.

Drug Dev. Res., 25, 249-265 (1992)).

The use of non steroidal antiinflammatory compounds (NSAIDs) in the treatment of inflammation and as analgesics and antiarthritics, etc. is widespread and well documented (C.S. Boynton, et al., J. Clin. Pharmacol., 28, 512-517 (1988))). On the other hand, the risks involved in the use of these compounds have also extensively been described (K.D. Rainsford, Agents & Actions, 7, 573-577 (1977); J.F. Fries et al., Gastroenterology, 96, 647-655 (1989)) and Henry D. et al., Br. Med. J., 312, 1563 (1996)). The therapeutic use thereof involves undesired effects on the gastrointestinal tract, such as bleeding, erosions, gastric and intestinal ulcers and the like, a relationship existing between the therapeutic effect and the gastrointestinal lesions (B.R.J. Whittle et al., Gastroenterology, 80, 94-98 (1981)).

Traditional NSAIDs are generally equipotent inhibitors of both isoenzymes COX-I and -II (E.A. Meade et al., J. Biol. Chem., 268, 6610-6614 (1993) and J.A. Mitchell et al., Proc. Nat. Acad. Sci. USA, 90, 11693-11697 (1993)). The selective inhibition of COX-II has recently been proved to provide drugs with antiinflammatory, antipyretic and analgesic activities comparable with conventional NSAIDs but, apparently, with a lower incidence of some gastrointestinal undesired effects (J.L. Masferrer et al., Proc. Nat. Acad. Sci. USA, 91, 3228-3232 (1994); C.C. Chan et al., J. Pharmacol. Exp. Therap., 274, 1531-1537 (1995); R.C. Hubbard, Arthritis & Rheumatism., 39 (9) Suppl. S226 (1996) and E. Ehrich, Arthritis & Rheumatism., 39-

(9) Suppl. S81 (1996))).

The incidence of disturbances in the gastric and intestinal mucosa, such as gastrointestinal ulcers, intestinal inflammation, Crohn's disease or ulcerative colitis, gastritis, local enteritis, diverticulitis, etc, occurs in a remarkable part of the population, in most cases with complications, such as perforation of mucosa, hemorrhage, etc (L. García-Rodríguez et al., Lancet, 343, 769-772 (1994)). The treatment of these patients with pre-existent disorders with conventional NSAIDs causes additional undesired effects related with the increase in the number and in the severity of ulcers or with the delay in its natural healing process (J.L. Wallace et al., Gastroenterology, 102, 18-27 (1992) and A.H. Soll, et al. Ann. Intern. Med., 114, 307-319 (1991)). Compounds useful in the treatment of inflammatory diseases and pain which could also be used in patients with this type of disorders are therefore in great demand.

Different approaches have been suggested aiming at obtaining compounds which have antiinflammatory and analgesic activities and at the same time do not increase neither worsen any pre-existent gastrointestinal disorders in some patients. Among these approaches should be underlined the use of nitrous oxide (NO) donor compounds, of COX-II selective inhibitors and of compounds with a structure having both characteristics.

As far as the first class of NO donor compounds is concerned, these compounds have been described to promote the natural healing process of ulcers in animal-

models with gastric ulcers (A. Schmassmann et al., Gastroenterology, 110 (4) Suppl. A252 (1996)). Nevertheless, this property is not expressed in the presence of traditional NSAIDs, therefore the combined administration of both drugs does not seem beneficial.

As for the use of cyclooxygenase-II selective inhibitors, the advantages deriving from their lower lesive effects on the gastrointestinal tract and on kidney have already been described in tests on healthy animals. On the contrary, the use of cyclooxygenase-II inhibitors in animal models with pre-existent gastrointestinal lesions provides no such beneficial effects. Thus, the use of these compounds in animal models with gastric ulcer delays their natural healing process, as it happens with traditional NSAIDs (A. Schmassmann et al., Gastroenterology, 110 (4) Suppl. A252 (1996) and B.M. Peskar et al., Prostagl. Leukotr. and Ess. Fatty Acids, 55 (1) 45 (1996)). On the other hand, some of these COX-II selective inhibitors, that have clearly shown to be beneficial in the treatment of healthy animals (A. Ford-Hutchinson et al., WO-94/13635 (1994)), were found to increase, in rats with induced ulcerative colitis, the incidence and the severity of the lesions, as well as the mortality rate therefrom (B.K. Reuter et al., J. Clin. Invest., 98 (9) 2076-2085 (1996)).

Finally, compounds having both characteristics, i.e. an aryl propionate or acetate structure (traditional cyclooxygenase inhibiting NSAIDs) as well as an NO donor group (nitroxyalkyl type) are described in literature (J.L. Wallace, G. Cirino, TiPS, 15, 405

(1996)). These compounds have shown reduced renal damage and gastrolesivity than the related NSAIDs in a number of animal models (J.L. Wallace et al., Eur. J. Pharmacol., 257, 249-255 (1994)). Nevertheless, in animal models with pre-existent gastrointestinal ulcers, these compounds showed no advantages as therapeutical agents. Thus, in gastric ulcer bearing rats, these compounds delay the ulcer natural healing process (A. Schmassmann et al., Gastroenterology, 110 (4) Suppl. A252 (1996)).

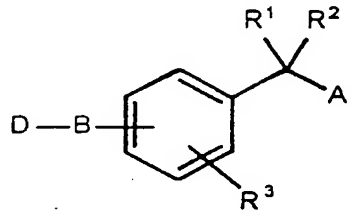
What stated above evidently shows the need for compounds useful in the treatment of inflammation and pain which could also be used in patients with ulcers and pre-existent disorders of the gastrointestinal tract.

The compounds of the present invention, defined by the formula I, are cyclooxygenase-I inhibitors, while having a poor activity on cyclooxygenase-II. How it is to be expected from their action at the cellular level, these compounds are analgesics and antinflammatories in in vivo animal models. Surprisingly, the cyclooxygenase-I selective compounds lack the characteristic gastrointestinal side-effects of non-selective NSAIDs as well as those of the cyclooxygenase-II inhibitors. Thus, in animal models with gastrointestinal lesions and disorders, the compounds I neither worsen ulcers or erosions, nor increase their incidence or delay their healing. Such a surprising behaviour could not be foreseeable in view of the commonly established assumptions ascribing the activities of function modulation and protection of the gastric and intestinal

mucosa to COX-I and the inflammatory processes to COX-II in that, according to such assumptions, the inhibition of the latter should a priori be preferable for the preparation of therapeutically valuable compounds.

DISCLOSURE OF THE INVENTION

The present invention relates to compounds of general formula I,



I

wherein:

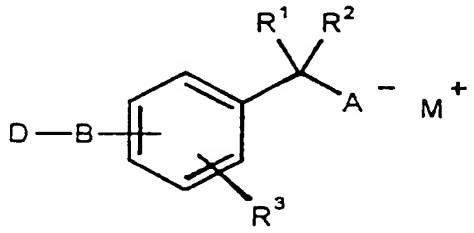
- A is a $-COOR^4$, $-SO_3R^4$, $-SO_2NHCOR^4$, $-SO_2NHCOOR^4$, $-SO_2NHCONHR^4$, $-CONHOR^4$, $-CON(OH)R^4$, $-N(OH)CONH_2$, $-N(OH)COR^4$, $-CONHSO_2R^5$ group or a 5-tetrazolyl group;
- B is a single bond or a diradical which represents a (C_1-C_4)-alkyl or alkenyl group, a -CO- group, an oxygen atom, a sulfur atom, a NR^4 group, a $-CON(R^4)-$ group or a $-N(R^4)CO-$ group;
- D is hydrogen, a (C_1-C_6)-alkyl, alkenyl or alkynyl group, a (C_3-C_7)-cycloalkyl or cycloalkenyl group, all these groups optionally having one or more hydrogen atoms substituted by halogen atoms, hydroxy groups, (C_1-C_4)-alkoxide groups or (C_1-C_4)-alkyl groups;
- R^1 and R^2 are independently hydrogen, (C_1-C_6)-alkyl or (C_3-C_6)-cycloalkyl or, taken together, they form

a (C_3-C_6)-cycloalkyl;

- R^3 is hydrogen, fluorine, chlorine, bromine, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxide;
- R^4 is hydrogen, a (C_1-C_4)-alkyl or a phenylakyl group of less than 10 carbon atoms;
- R^5 is the same as R^4 except hydrogen,

provided that the compound of formula I is other than:
3-chloro-4-(2-propenyloxy)benzeneacetic acid;
α-methyl-4-[(2-methyl-2-propenyl)amino]benzeneacetic acid;
α-methyl-4-(2-methylpropyl)benzeneacetic acid;
4-(2-methylpropyl)benzeneacetic acid;
and N-hydroxy-α-methyl-4-(2-methylpropyl)benzeneacetamide.

The present invention also relates to the pharmaceutically acceptable salts and solvates of the compounds of formula I, and in particular the salts represented by the formula Ia,



Ia

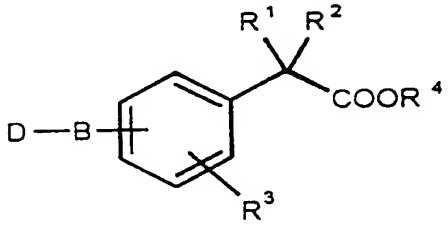
wherein M^+ is an alkali metal cation (e.g. Na^+, K^+), or the half amount of an alkaline-earth metal cation (e.g. 1/2 Ca^{2+}, 1/2 Mg^{2+}), or it represents a cation derivative of an amine or ammonium quaternary salt (e.g. triethylammonium, tris(hydroxyethyl)methylammonium).

The compounds of formula I can have one or more asymmetric carbons in their structure. The present

invention comprises all the possible stereoisomers as well as the mixtures thereof.

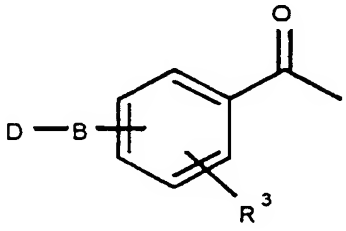
According to the present invention, the compounds of general formula I can be obtained through any one of the following processes:

a) A compound of formula IIa,



IIa

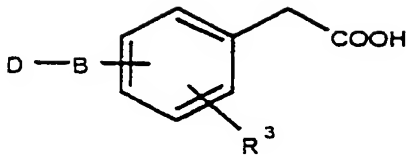
i.e. of general formula I where A is $COOR^4$, wherein D, B, R^1, R^2, R^3 and R^4 represent the groups defined above, can be obtained by reaction of a compound of general formula III,



III

with sulfur and morpholine in the usual conditions for the Willgerodt-Kindler reaction, namely at a temperature ranging between 80°C and reflux of the amine for a time from 4 to 48 hours, followed by hydrolysis of the resulting thioamide by treatment with a mixture of sulfuric acid, acetic acid and water at the reflux temperature, for a time ranging between 12 and 48 h. The

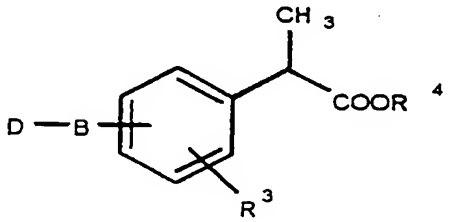
resulting compound IV



IV

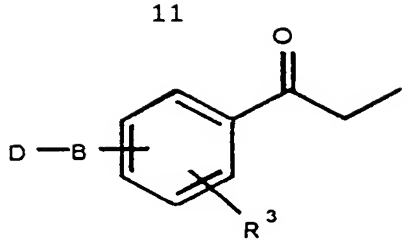
corresponds to IIa where $R^1=R^2=R^4=H$, or it is transformed into IIa, where $R^1=R^2\neq H$ or $R^1=H$ and $R^2\neq H$, by protecting the carboxylic acid group by esterification with methanol, ethanol or benzyl alcohol in acidic medium following the usual synthetic processes, and subsequently by alkylating the resulting ester by treatment with a strong base such as lithium diisopropylamide at a temperature ranging from -80°C to -50°C for a time ranging between 2 and 12 h in the presence of hexamethylphosphoramide (HMPA) and of the necessary equivalents of the corresponding alkyl iodide (R^2-I).

b) Alternatively, a compound of formula IIb,



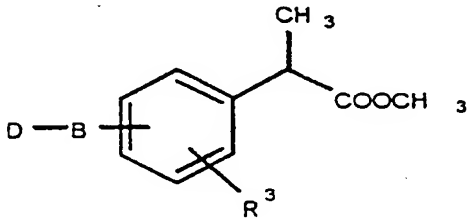
IIb

i.e. of general formula I where A is $COOR^4$ and $R^1=H$ and $R^2=CH_3$, wherein D, B, R^3 and R^4 represent the groups defined above, can be obtained by reaction of a compound of formula V,



V

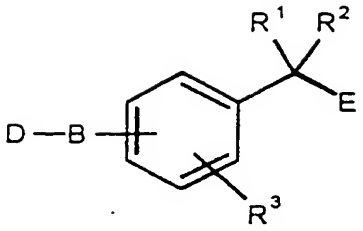
with thallium nitrate (III) trihydrate and methyl orthoformate in a suitable solvent, such as methanol, at the solvent reflux temperature and for a time ranging from 2 to 24 h, followed by hydrolysis of the resulting ortho ester in acidic medium, for example by treatment with catalytic amounts of p-toluenesulfonic acid in a suitable solvent such as acetone or tetrahydrofuran at the solvent reflux temperature for 1 to 18 h. The resulting compound VI



VI

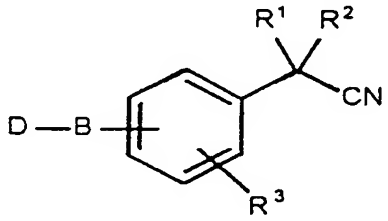
corresponds to IIb where R^4 is a methyl group or is converted to IIb where R^4 is hydrogen by saponification of the methyl ester by treatment with a suitable base, such as lithium or sodium hydroxide in aqueous solution in a suitable organic solvent, such as methanol, ethanol or tetrahydrofuran, at a temperature ranging between 20°C and the solvent reflux for a time between 1 and 48 hours.

c) A compound of formula IIc,



IIc

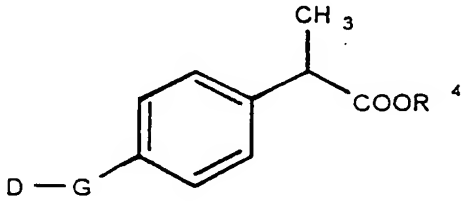
i.e. of general formula I where A is E, wherein E represents the COOH or 5-tetrazolyl groups and D, B, R^1, R^2 and R^3 represent the groups defined above, can be obtained starting from a compound VII,



VII

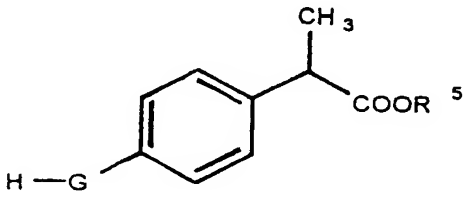
or, when E is COOH, by hydrolysis of the nitrile group, for example, with a 35% NaOH aqueous solution in ethanol at a temperature ranging from 25°C to the solvent reflux for 2-48 h, or, when E is a 5-tetrazolyl group, by treatment, for example, with azidotributyltin in a suitable high-boiling solvent such as N,N-dimethylformamide at a temperature from 80°C to the solvent reflux for a time between 2 and 48 h.

d) A compound of formula IId,



IId

i.e. of general formula I where R^1 and R^3 are hydrogen, R^2 is a methyl group, A is $COOR^4$ and B is a G group bound to the phenyl group at the *para* position to the propionate substituent, wherein G represents an oxygen or sulfur atom, a NR^4 group and D and R^3 represent the groups described above, can be prepared starting from a compound of formula VIII,



VIII

wherein R^3, R^5 and G represent the groups defined above, commercial or easily available following simple chemical processes, by alkylation reaction of the heteroatom contained in G with a compound IX,

D —X

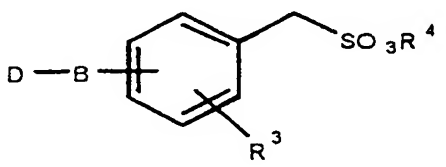
IX

where X is a chlorine or bromine atom or an alkyl or aryl sulfonate group. The reaction between VIII and IX when G is an amino group is carried out by treatment of a compound VIII with an excess of IX where X is bromine at a temperature from 60 to 170°C for a time between 4 and 24 h. When G is sulfur, the reaction is carried out subjecting compound VIII to the action of a base such as a metal hydroxide or carbonate and subsequently reacting it with a compound IX in a suitable organic solvent such as N,N-dimethylformamide, ethanol or methanol at a temperature ranging between 0° and 100°C and for a time

between 2 and 24 hours. When G is oxygen, the reaction can be carried out in the presence of a base such as a metal hydride, in a suitable solvent, such as N,N-dimethylformamide, tetrahydrofuran or benzene, at a temperature ranging between 25° and 120°C and for a time from 4 to 24 hours. Alternatively, when G is oxygen, a compound IId can be obtained by reaction between a compound VIII and a compound IX in the general conditions of the Mitsunobu reaction; i.e., in the presence of diethyl azodicarboxylate and triphenylphosphine in a suitable solvent such as tetrahydrofuran at room temperature and for a time between 24 and 72 hours.

e) A compound of general formula I where A is a $CONHOR^4$, $CON(R^4)OH$ or $CONHSO_2R^5$ group can be obtained starting from a compound IIa where R^4 is hydrogen by reaction of the acid chloride IIa, obtained, for example, by treatment with oxalyl chloride under reflux for 0.5-4 hours, with a compound R^4ONH_2, $HONR^4$ or $R^5SO_2NH_2$, respectively, in the presence of an organic amine such as pyridine or triethylamine, in a suitable solvent such as tetrahydrofuran or N,N-dimethylformamide, at a temperature between 25°C and the solvent reflux temperature and for a time of 4-24 hours.

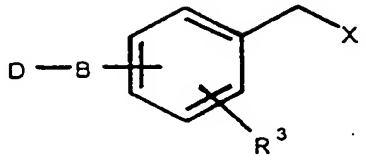
f) A compound of formula IIe,



IIe

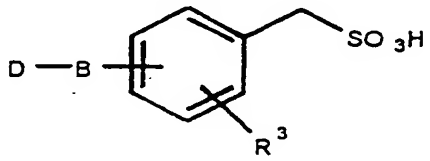
i.e. of general formula I where A is SO_3R^4 and R^1 and R^2

are hydrogen, wherein D, B, R^4 and R^3 represent the groups defined above, can be obtained starting from a compound X,



X

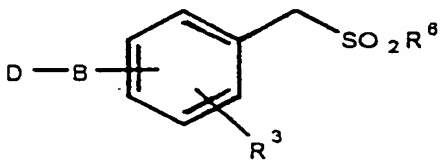
wherein D, B, R^3 and X represent the groups defined above, by reaction with sodium sulphite in a suitable solvent such as ethanol, 1,4-dioxane or N,N-dimethylformamide at a temperature ranging between 25°C and the solvent reflux and for a time between 1 and 24 h. The resulting compound XIa



XIa

corresponds to IIe where R^4 is hydrogen, or it is converted to IIe where R^4 is different from hydrogen by esterification of XIa in the usual conditions for the esterification of sulfonic acids.

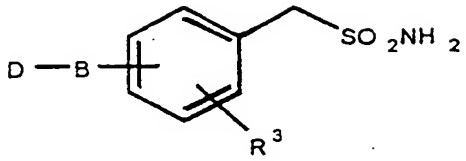
g) A compound of formula IIf,



IIe

i.e., of general formula I where A is SO_2R^6 and R^1 and R^2 are hydrogen, wherein D, B, and R^3 represent the groups defined above, and R^6 represents a $-NHCOR^4$,

-NHCOOR^4 or -NHCONHR^4 radical, can be obtained starting from a compound XIb,

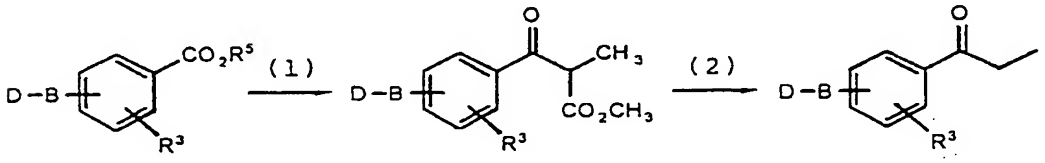


XIb

by reaction with a compound R^{4}COCl, R^{4}OCOCl or R^{4}NCO, respectively, according to the type of radical represented by R^6, in the usual conditions for the synthesis of sulfonylamides, sulfonylcarbamates and sulfonylureas, respectively.

A starting compound of general formula V can be obtained, for example, starting from a compound XII following the process described in scheme 1

Scheme 1



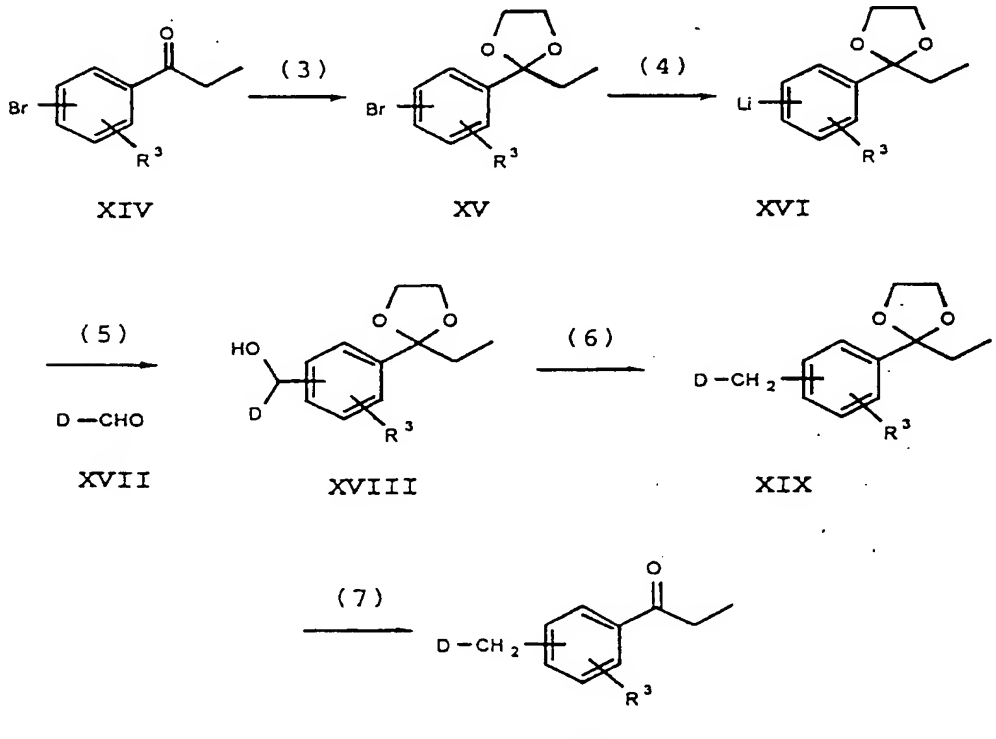
XII XIII V

In this sequence, a compound XIII is obtained by reaction of a starting compound XII with methyl propionate in the presence of a base, such as a metal hydride, in a suitable solvent such as xylene, toluene or tetrahydrofuran at a temperature between 80 and 140°C for a time between 3 and 24 h (step 1). A compound V is obtained by hydrolysis and decarboxylation in acidic medium of a compound XIII using, for example, a mixture of acetic acid and hydrochloric acid at the reflux temperature of the mixture and for a time ranging

between 4 and 24 h (step 2).

Alternatively, a starting compound of formula Va, i.e. of general formula V where B is a methylene group can be obtained, for example, through the process which is showed in scheme 2.

Scheme 2



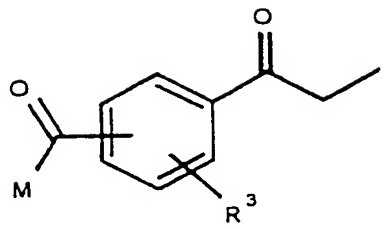
In this sequence, a compound XV is obtained by protection of the carbonyl group of a compound XIV, commercial or easily available through simple chemical processes, with ethylene glycol in the presence of catalytic amounts of p-toluenesulfonic acid in a suitable solvent in which the azeotropical removal of the water is possible, such as benzene or toluene, at the solvent reflux temperature and for a time ranging between 5 and 24 h (step 3).

A compound of formula XVIII is obtained preparing the organolithium derivative XVI by treating XV with n-butyllithium or *tert*-butyllithium at -78°C in an inert solvent such as ethyl ether or tetrahydrofuran for a time between 1 and 4 h (step 4), and reacting it immediately with an aldehyde XVII for a time between 4 and 24 h at a temperature between 0 and the solvent reflux (step 5).

A compound of formula XIX can be obtained by direct catalytic hydrogenation of a compound XVIII with 10% palladium-on-charcoal in a suitable solvent such as dichloromethane, ethyl acetate, ethanol or mixtures thereof, optionally in the presence of a weak acid, such as acetic acid, at room pressure and temperature and for a time from 8 to 24 h (step 6). Alternatively, the hydroxy group of compound XVIII can be activated before the hydrogenolytic process by formation of an acetate, obtainable by treatment of compound XVIII with acetic anhydride in the presence of an organic base such as triethylamine in a suitable solvent such as chloroform or tetrahydrofuran at a temperature between 25°C and the solvent reflux.

A compound Va is obtained by treatment in acidic medium of a compound XIX, for example, with sulfuric acid or hydrochloric diluted or concentrated acid, in a solvent such as tetrahydrofuran or ethanol at a temperature between the room temperature and the solvent reflux for a time between 2 and 18 h (step 7).

Alternatively, a compound of formula Vb



Vb

i.e. of general formula V where B is a carbonyl group and D is an M group, wherein R^3 represents the groups defined above and M is an aromatic or heteroaromatic group, can be obtained by reaction of the organolithium compound XVI with a compound XX,

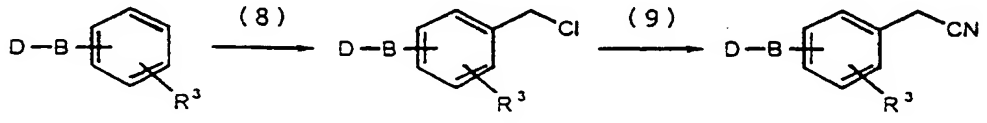
D-CN

XX

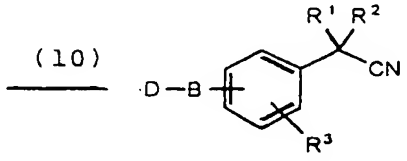
in the conditions described above for the preparation of XVIII starting from XVII and XVI (step 5), followed by hydrolysis in acidic medium in the conditions described for the preparation of Va starting from XIX (step 7).

A starting compound of formula VII can be obtained starting from a compound XXI through the process which is showed in scheme 3.

Scheme 3



XXI XXII XXIII



VII

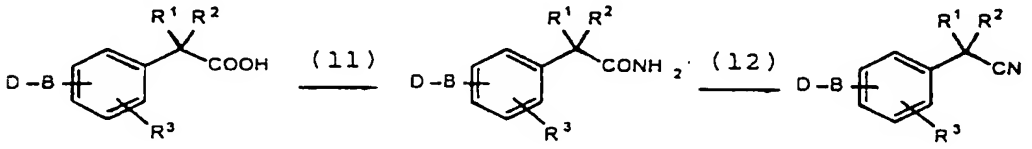
A compound of formula XXII can be obtained starting

from a compound XXI, commercial or easily obtainable through simple chemical processes, by chloromethylation with formaldehyde and hydrogen chloride in the presence of catalytic amounts of zinc chloride (II) or of aluminium trichloride or, alternatively, by reaction of XXI with paraformaldehyde and acetamide in the presence of a strong acid such as concentrated sulfuric acid at a temperature from 40 to 110°C for a time between 4 and 18 h, and subsequent treatment of the resulting acetamide with phosphorous oxychloride in N,N-dimethylformamide at the solvent reflux temperature and for a time between 0.5 and 5 h (step 8).

A compound XXIII is obtained starting from a compound XXII by substitution of the chlorine atom by a cyano group with sodium or potassium cyanide in tetrahydrofuran, DMSO or ethanol at a temperature between 25°C and the solvent reflux (step 9). The obtained compound XXIII can be transformed into a compound VII by sequential alkylation with a suitable alkyl halide in the conditions described above for the preparation of IIa starting from IV (step 10).

Alternatively, when a compound of formula XXIV, commercial or easily available through similar chemical processes, a compound of formula VII can be obtained starting from XXIV, i.e. of formula IIc where E is COOH, following the process described in the scheme 4.

Scheme 4



XXIV XXV VII

In this sequence, a compound XXV can be obtained by aminolysis with gaseous ammonia of a compound XXIV previously activated in the form of a mixed anhydride with a suitable chloroformate. In this way, the compound XXIV is reacted with ethyl chloroformate in the presence of an organic base such as triethylamine in a solvent such as tetrahydrofuran at room temperature for a time between 1 and 4 h, and the resulting anhydride is bubbled with gaseous ammonia in the presence of methanol or ethanol acting as solvents of the gas (step 11). Compound VII is obtained by dehydration of carboxamide XXV, for example, with phosphorous oxychloride in a solvent such as N,N-dimethylformamide at a temperature from 0° to 50°C and for a time ranging between 3 and 24 hours (step 12).

A compound XIb can be obtained starting from a compound XIa, by previously preparing the compound XIa acid chloride by treatment with, for example, phosphorous pentachloride, phosphorous trichloride or thionyl chloride in an inert solvent at a temperature from 25° to 80°C for a time between 1 and 24 hours and, after that, reacting the resulting sulfonic acid chloride with gaseous ammonia in a suitable solvent such as ethanol or methanol or mixtures thereof with a miscible solvent in which the product is soluble at room temperature for a time between 2 and 72 hours.

The compounds of general formula I, object of the present invention, not only show a high inhibitory activity on cyclooxygenase-I, but also a marked selectivity for this isoenzyme vs. cyclooxygenase-II. Surprisingly, these compounds also proved to have

antiinflammatory, antirheumatic and analgesic activities. Furthermore, in animal models with pre-existent ulcers and gastrointestinal disorders, they neither worsen the ulcers or erosions of the gastrointestinal mucosa, nor increase their incidence or severity, or delay the healing thereof. The behaviour of these compounds could not be foreseeable in view of the commonly established assumptions ascribing the activities of function modulation and protection of the gastric and intestinal mucosa to COX-I and the inflammatory processes to COX-II in that, according to such assumptions, the inhibition of the latter should a priori be preferable for the preparation of therapeutically valuable compounds.

The enzymatic activity referred to in the present invention is illustrated by the capability of these compounds of inhibiting the production of thromboxanes (TxB_2) in human polymorphonuclear neutrophils (through cyclooxygenase-I inhibition) as well as of prostaglandins (PGE_2) in human monocytes stimulated with lipopolysaccharide (evaluation of the possible inhibition of cyclooxygenase-II). IC_{50} values correspond to the μM inhibitory concentration necessary to reduce by 50% (compared with the control) the production of the concerned mediator. As a comparison, the IC_{50} values inhibiting cyclooxygenase-I and cyclooxygenase-II corresponding to (+)-S-ibuprofen are 0.15 μM and >1 μM, respectively, whereas for indomethacin IC_{50} are 0.19 μM and 0.0056 μM, respectively.

The present invention also relates to the use of the compounds of general formula I in pharmaceutical

compositions useful for the inhibition of cyclooxygenase or for the treatment of disorders related with this enzyme. More specifically, the present invention relates to the use of these compounds in pharmaceutical compositions useful for the selective inhibition of cyclooxygenase-I or for the treatment of disorders related with this enzyme. In this invention, by compounds useful for the "selective inhibition of cyclooxygenase-I" those compounds are meant which have *in vitro* or *in vivo* a cyclooxygenase-II *vs.* cyclooxygenase-I IC_{50} values ratio higher than or equal to 10.

Due to their pharmacological characteristics as well as to their toxicologic profile, the compounds of general formula I of this invention are a new rational approach to the treatment of inflammation, rheumatism and pain, which can be also used in patients with pre-existent gastrointestinal disorders as these compounds have, in addition to their therapeutical activity, a reduced capability of causing additional undesired effects which would increase the severity of ulcers or delay the natural healing process thereof. Furthermore, the compounds of the invention, due to the above cited pharmacological characteristics and toxicologic profile thereof, are useful as an alternative to the use of conventional NSAIDs, including those cases in which the latter can be contra-indicated, as it happens in patients with gastrointestinal ulcers or with relapses of gastric lesions, gastric bleeding and coagulation problems.

More specifically, the invention further relates to

the use of compounds I for the preparation of pharmaceutical compositions useful in the treatment of pain or fever associated with rheumatic fever, lumbar and cervical pains, viral infections, dysmenorrhea, headache or toothache, myositis, neuralgia, synovitis, arthritis including osteoarthritis and rheumatoid arthritis, ankylosing spondylitis, bursitis and burns, or in the treatment of diseases of inflammatory or allergic origin, such as allergic rhinitis, allergic conjunctivitis, rheumatoid arthritis, osteoarthritis, tendinitis, bursitis or psoriasis and, most specifically, to the therapeutical use in patients with gastrointestinal disorders pre-existent to the treatment, for example in patients with gastrointestinal ulcers, intestinal inflammatory diseases, Crohn's disease or ulcerative colitis, gastritis, local enteritis and diverticulitis, as well as in patients with relapses of gastric lesions, gastric bleeding and coagulation problems.

EXAMPLES

The following examples further illustrate the preparation of the compounds of the present invention.

Example 1: 5-[1-[4-(Isopropylamino)phenyl]ethyl]-1*H*-tetrazol

1A 2-(4-Nitrophenyl)propionamide

A solution of 2-(4-nitrophenyl)propionic acid (10 g, 51.3 mmol) in tetrahydrofuran (80 ml) is added, in succession, with triethylamine (14.3 ml, 0.10 mol) and ethyl chloroformate (9.8 ml, 0.10 mol), then stirred at room temperature for 2 h. After that methanol (80 ml) is added and gaseous ammonia is bubbled for 0.5 h,

subsequently leaving under stirring at room temperature for 4 h. The volatiles are evaporated off under reduced pressure and the residue is diluted with ethyl acetate (150 ml), washing in succession with a 1M HCl solution, a 5% potassium bicarbonate solution and a sodium chloride saturated solution. The organic phase is dried and the solvent is evaporated off under reduced pressure to obtain 9.66 g of the title compound (97% yield).

1B 2-(4-Nitrophenyl)propanonitrile

Phosphorous oxychloride (30 ml) is added very slowly at 0°C to dry N,N-dimethylformamide (350 ml) and the mixture is stirred at room temperature for 35 minutes. After that, a solution of 2-(4-nitrophenyl)propionamide (9.5 g, 48.97 mmol) in N,N-dimethylformamide (15 ml) is added, stirring at room temperature for 18 h. After this time, the reaction mixture is poured on an ice-water mixture (100 ml), extracted with ethyl acetate and dried. The solvents are evaporated off under reduced pressure to obtain a residue which is purified by column chromatography on silica gel. Eluting with hexane:chloroform, 4:1, 7.26 g of the title compound are obtained (84% yield).

1C 2-(4-Aminophenyl)propanonitrile

A solution of 2-(4-nitrophenyl)propanonitrile (7.1 g, 40.34 mmol) in ethanol (80 ml) is added with 5% palladium-on-charcoal (0.40 g) and stirred at room temperature for 4 h, under hydrogen atmosphere. The catalyst is filtered off and the solvent is evaporated off the filtrate under reduced pressure, thereby obtaining 5.37 g of the title compound (91% yield).

1D 2-(4-Isopropylamino)propanonitrile

A mixture of 2-(4-aminophenyl)propanonitrile (5.30 g, 36.3 mmol), 2-bromopropane (2.23 g, 18.2 mmol) and chloroform (5 ml) is refluxed for 8 h, then is evaporated to dryness and the residue is partitioned between a mixture of ethyl acetate and of a 5% potassium carbonate solution. The aqueous phase is extracted with ethyl acetate, the combined organic extracts are washed with a sodium chloride saturated solution, dried and the solvent is evaporated off under reduced pressure. The resulting crude is purified by column chromatography on silica gel deactivated with triethylamine. Eluting with hexane:ethyl acetate, 1:1, 1.85 g of the title compound are obtained (54% yield). Eluting with ethyl acetate 2.93 g of the starting aniline are recovered.

1E 5-[1-[4-(Isopropylamino)phenyl]ethyl]-1*H*-tetrazol

A suspension of 2-(4-isopropylamino)propanonitrile (2.81 g, 14.95 mmol), azidotributyltin (12.12 ml, 44.2 mmol) and N,N-dimethylformamide (162 ml) is heated at 110°C for 24 h under nitrogen atmosphere. Subsequently the mixture is concentrated under vacuum, the residue is suspended in ethanol (100 ml), added with 1M hydrochloric acid (30 ml) and stirred at room temperature for 30 minutes. Ethanol is evaporated off under reduced pressure and the aqueous residue is partitioned between an ethyl acetate:water mixture, adjusting the aqueous phase to pH 6 with a sodium carbonate saturated solution. The aqueous phase is extracted with ethyl acetate and the combined organic phases are dried and evaporated under reduced pressure. The resulting residue is purified by crystallization

from ethanol, to obtain 2.02 g of the title compound (58% yield).

Example 2: 2-[4-(Isobutylsulfinyl)phenyl]propionic acid

2A O-ethyl and S-[4-(1-cyanoethyl)phenyl] dithiocarbonate

A solution of 2-(4-aminophenyl)propanonitrile (2.81 g, 19.24 mmol) in ethanol (50 ml) and 12M HCl (30 ml) is added at 0°C with a solution of sodium nitrite (1.457 g, 21.0 mmol) in water (2 ml) and is left at 0°C for 30 minutes. After that, a solution of potassium ethylxanthate (6.17 g, 38.5 mmol) in water (10 ml) is added slowly in 10 minutes. When the addition is completed, the mixture is stirred at 45°C for 18 h, then diluted with water (150 ml) and extracted with ethyl acetate. The combined organic phases are washed with a sodium chloride saturated solution, dried and the solvent is evaporated off under reduced pressure. The resulting residue is purified by column chromatography eluting with hexane:ethyl acetate, 9:1, thereby obtaining 1.70 g of the title compound (35% yield).

2B 2-(4-Mercaptophenyl)propionic acid

A solution of O-ethyl and S-[4-(1-cyanoethyl)phenyl] dithiocarbonate (1.70 g, 6.77 mmol) in ethanol (247 ml) is added with 35% NaOH (90 ml) and stirred under reflux for 4 h, then acidified with 1M HCl and the volatiles are evaporated off. The residue is extracted with ethyl acetate. The organic phase is dried and the solvent is evaporated off under reduced pressure, to obtain 0.939 g of the title compound (76% yield).

2C 2-(4-Isobutylthiophenyl)propionic acid

A solution of 2-(4-mercaptophenyl)propionic acid (0.939 g, 5.15 mmol) in ethanol (20 ml) is added with potassium carbonate (1.463 g, 10.3 mmol), then with 1-bromo-2-methylpropane (0.706 g, 5.15 mmol). The resulting mixture is stirred under reflux for 2 h, subsequently it is left to cool, evaporated to dryness and the residue is partitioned between a mixture of a 1M hydrochloric acid solution and ethyl acetate. The aqueous phase is extracted with ethyl acetate, the combined organic phases are washed with a sodium chloride saturated solution, dried and the solvent is evaporated off under reduced pressure, thereby obtaining 1.11 g of the title compound (91% yield).

2D 2-[4-(Isobutylsulfinyl)phenyl]propionic acid

A solution of 2-(4-isobutylthiophenyl)propionic acid (1.0 g, 4.20 mmol) in methanol (15 ml) is added with 1 ml of a solution prepared mixing 2-propanol (3 g) and conc. sulfuric acid (0.15 ml), then stirred for 15 minutes at room temperature. After that, 30% H_2O_2 (0.90 ml) is added and the resulting mixture is stirred at room temperature for 1 h, then poured on a sodium chloride saturated solution (25 ml) and extracted with ethyl acetate. The combined organic extracts are dried, evaporated under reduced pressure and the residue is purified by column chromatography on silica gel. Eluting with chloroform:methanol, 98:2, 0.760 g of the title compound are obtained (71% yield).

Example 3: 2-[2-Fluoro-4-(isopropyloxy)phenyl]-propionic acid

3A Ethyl 2-fluoro-4-hydroxybenzoate

A solution of 2-fluoro-4-hydroxybenzonitrile (10.0 g, 73.0 mmol) in absolute ethanol (250 ml) is added with conc. sulfuric acid (50 ml) and stirred under reflux for 18 h. After this time, the volatiles are evaporated off under reduced pressure and the resulting residue is neutralized with a sodium bicarbonate saturated solution and extracted with ethyl ether (4x100 ml). The solvent is dried and evaporated off under reduced pressure, to obtain 12.5 g of the title compound (93% yield).

3B Ethyl 2-fluoro-4-isopropyloxybenzoate

A mixture of ethyl 2-fluoro-4-hydroxybenzoate (6.12 g, 33.3 mmol), 2-propanol (5.10 ml, 66.6 mmol) and triphenylphosphine (13.1 g, 50.0 mmol) in anhydrous tetrahydrofuran (185 ml) is added with diethyl azodicarboxylate (7.86 ml, 50 mmol). The resulting mixture is stirred at room temperature for 36 h. After that, ethyl ether (500 ml) is added and the mixture is left to crystallize for 24 hours at 0°C. After that the solid is filtered and the filtrate is washed in succession with hydrochloric acid 0.2 M, 5% sodium bicarbonate and with a sodium chloride saturated solution. After drying and evaporating off the solvent under reduced pressure, a residue is obtained which is purified by column chromatography on silica gel eluting with petroleum ether:chloroform mixtures of increasing polarity, thereby obtaining 5.27 g of the title compound (70% yield).

3C 2-Fluoro-4-isopropyloxypropiophenone

A suspension of sodium hydride (60% dispersion in mineral oil, 3.76 g, 94 mmol) in xylene (20 ml) is added

under nitrogen atmosphere with a solution of ethyl 2-fluoro-4-isopropyloxybenzoate (5.0 g, 22.1 mmol) in xylene (25 ml) and the resulting mixture is heated to the solvent reflux temperature. After that, methyl propionate (9.5 ml, 94.3 mmol) is added in 3 hours and, when the addition is completed, the resulting mixture is kept under stirring at the reflux temperature for a further 3 h. Subsequently the mixture is cooled on an ice-bath and added slowly with a 10% ammonium chloride solution (40 ml), then with a 6M HCl solution (40 ml). The phases are separated and the aqueous one is extracted with ethyl ether. The combined organic phases are dried and the solvent is evaporated off under reduced pressure.

The resulting residue is suspended in a mixture of glacial acetic acid (10 ml) and a 6M HCl solution (65 ml) and stirred under reflux for 16 h. The mixture is cooled, added with water (25 ml), extracted with ethyl ether. The combined ether phases are washed with a 3M sodium hydroxide solution and dried and the solvent is evaporated off under reduced pressure. The residue is redissolved in dimethoxyethane (15 ml) and added, in succession, with water (10 ml) and with potassium hydroxide (1.0 g). After 1 h stirring at the reflux temperature, the mixture is left to cool, extracted with ethyl ether, the combined organic phases are washed with water, dried and the solvent is evaporated off under reduced pressure. The resulting residue is purified by column chromatography on silica gel eluting with hexane:ethyl ether mixtures of increasing polarity, thereby obtaining 2.92 g of the title compound (63%

yield).

3D 2-[2-Fluoro-4-(isopropyloxy)phenyl]methyl propionate

A solution of thallium nitrate (III) trihydrate (6.67 g, 14.1 mmol) in a methanol and trimethyl orthoformate 1:1 mixture, (40 ml) is added with a suspension of 2-fluoro-4-isopropyloxypropiophenone (2.75 g, 13.1 mmol) in a methanol and trimethyl orthoformate 1:1 mixture (20 ml). The resulting mixture is stirred under reflux for 5 h, cooled, the formed solid is filtered and the filtrate is evaporated to dryness. The resulting residue is redissolved in dry acetone (50 ml) and added with a catalytic amount of p-toluenesulfonic acid, stirring under reflux for 3 h. Subsequently acetone is evaporated off under reduced pressure and the resulting crude is partitioned between water:ethyl acetate. The aqueous phase is extracted with ethyl acetate, the combined organic phases are washed with a sodium chloride saturated solution, dried and the solvent is evaporated off under reduced pressure. The residue is purified by column chromatography on silica gel, eluting with hexane:ethyl acetate mixtures of increasing polarity, thereby obtaining 2.04 g of the title compound (65% yield).

3E 2-[2-Fluoro-4-(isopropyloxy)phenyl]propionic acid

A mixture of 2-[2-fluoro-4-(isopropyloxy)phenyl]methyl propionate (2.0 g, 8.33 mmol), dimethoxyethane (10 ml) and a solution of 20% HCl (10 ml) is refluxed for 24 h, then diluted with water (20 ml) and extracted with ethyl acetate. The combined organic phases are washed with a sodium chloride saturated solution, then dried

and the solvent is evaporated off under reduced pressure, thereby obtaining 1.72 g of the title compound (91% yield).

Example 4: 2-[3-(Cyclopropylmethyl)phenyl]propionic acid

4A 2-(3-Bromophenyl)-2-ethyl-1,3-dioxolane

A mixture of 3'-bromopropiophenone (3.00 g, 14.1 mmol), ethylene glycol (2.3 ml), p-toluenesulfonic acid monohydrate (catalytic amount) and toluene (40 ml) is refluxed for 8 h in a Dean-Stark apparatus. After that, the reaction mixture is diluted with ethyl acetate (30 ml), washed, in succession, with a potassium carbonate saturated solution and with water, then dried and the solvents are evaporated off under reduced pressure. The resulting residue is purified by distillation under reduced pressure (boiling temperature 85-90°C at 0.5 Torr) to obtain 3.49 g of the title compound (93% yield).

4B 2-[3-[(1-Cyclopropyl-1-hydroxy)methyl]phenyl]-2-ethyl-1,3-dioxolane

A solution of 2-(3-bromophenyl)-2-ethyl-1,3-dioxolane (2.0 g, 7.78 mmol) in anhydrous tetrahydrofuran (10 ml) is added at -78°C and under inert atmosphere with 1.7 M *tert*-butyllithium in hexane (4.65 ml, 7.83 mmol) and stirred for 3 h. After that, a solution of cyclopropanecarboxyaldehyde (0.87 ml, 11.67 mmol) in anhydrous tetrahydrofuran (2 ml) is slowly added, the mixture is left to cool and kept under stirring for 18 h at 50°C. Subsequently the mixture is carefully added with water and extracted with ethyl ether. The combined organic phases are washed with a sodium chloride saturated solution, dried and the solvents are

evaporated off under reduced pressure, thereby obtaining 1.84 g of an oil which mainly contains the title compound and which is used directly in the following step without further purifications.

4C 1-[3-(Cyclopropylmethyl)phenyl]-1-propanone

The resulting crude from the previous step (1.84 g) is dissolved in a mixture of chloroform (10 ml), acetic anhydride (10 ml) and triethylamine (2 ml) and the resulting mixture is stirred under reflux for 5 h. After that the mixture is evaporated to dryness under reduced pressure and the resulting residue is partitioned between a mixture of a 1M HCl solution and ethyl acetate. The aqueous phase is extracted with ethyl acetate, dried and the solvent is evaporated off under reduced pressure. The resulting residue is dissolved in a mixture of ethyl acetate (10 ml), ethanol (10 ml) and acetic acid (5 ml), then added with 10% palladium-on-charcoal (271 mg). The resulting mixture is hydrogenated under atmospheric pressure for 18 h. The catalyst is filtered off and the solvents are evaporated off under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (20 ml) and added with a 50% sulfuric acid solution (10 ml). The mixture is refluxed for 6 h, then cooled to room temperature, diluted with water (30 ml) and extracted with chloroform. The combined organic phases are washed, in succession, with a potassium carbonate saturated solution and with water, dried and the solvents are evaporated off under reduced pressure. The resulting crude is purified by column chromatography on silica gel eluting with hexane:ethyl acetate mixtures of increasing polarity. Eluting with hexane:ethyl

acetate, 8:2, 0.749 g of the title compound are obtained (51% overall yield starting from 2-(3-bromophenyl)-2-ethyl-1,3-dioxolane).

4D Methyl 2-[3-(cyclopropylmethyl)phenyl]propionate

Following the process described in example 3 (point D), starting from 1-[3-(cyclopropylmethyl)phenyl]-1-propanone, the title compound is prepared (61% yield).

4E 2-[3-(Cyclopropylmethyl)phenyl]propionic acid

Following the process described in example 3 (point E), starting from methyl 2-[3-(cyclopropylmethyl)-phenyl]propionate, the title compound is prepared (81% yield).

Example 5: 2-(4-isobutyl-2-methoxyphenyl)butanoic acid

5A 3-(1-Hydroxy-2-methylpropyl)anisol

Following the process described in example 4 (point B), starting from 3-bromoanisol and isobutyroaldehyde, the title compound is prepared (86% yield).

5B 3-Isobutylanisol

Following the process described in example 1 (point C), by hydrogenating 3-(1-hydroxy-2-methylpropyl)anisol with 10% palladium-on-charcoal under atmospheric pressure in dichloromethane for 24 h, the title compound is prepared (77% yield).

5C 4'-Isobutyl-2'-methoxyphenylacetonitrile

A mixture of 3-isobutylanisol (5.0 g, 30.5 mmol), paraformaldehyde (0.92 g, 30.5 mmol) and conc. sulfuric acid (37 ml) is added with solid acetamide (5.4 g, 91.5 mmol). The reaction mixture is left at 60°C for 8 h, then poured carefully carefully on an ice-water mixture. The formed solid is recovered by filtration, digested with butyl acetate at 90°C, filtered and the filtrate is

evaporated to dryness. The resulting residue is dissolved in N,N-dimethylformamide (2 ml) and xylene (40 ml) and added with phosphorous oxychloride (2.84 ml, 30.5 mmol). The reaction mixture is heated at the reflux temperature for 1 h, then cooled, diluted with xylene (60 ml), washed with water, dried and evaporated to dryness under reduced pressure.

The resulting crude from the above step is suspended in a mixture of water (40 ml) and ethanol (100 ml) and added with sodium cyanide (1.79 g, 36.3 mmol), stirring under reflux for 4 h, then it is cooled to room temperature and added with ethyl ether (50 ml) and a sodium chloride saturated solution (50 ml). The two phases are separated and the aqueous phase is extracted with ethyl ether. The ether extracts are dried and the solvent is evaporated off, to obtain a crude which is purified by flash chromatography on silica gel column. Eluting with hexane:ethyl acetate, 3:2, 1.74 g of the title compound as a yellowish oil are obtained (27% yield).

5D 2-(4-Isobutyl-2-methoxyphenyl)butanonitrile

A solution of diisopropylamine (1.059 ml, 7.49 mmol) in anhydrous tetrahydrofuran (30 ml) under inert atmosphere at -78°C is added with a solution of 1.6 M n-butyllithium in hexane (4.29 ml, 6.88 mmol) and stirred at -78°C for 30 min. After that, the reaction mixture is slowly added with 4'-isobutyl-2'-methoxyphenyl-acetonitrile (1.27 g, 6.25 mmol) at -78°C and stirred at this temperature for 30 min. Subsequently, hexamethylphosphoramide (HMPA) (1.072 ml, 6.13 mmol) and ethyl iodide (0.50 ml, 6.25 mmol) are added, in

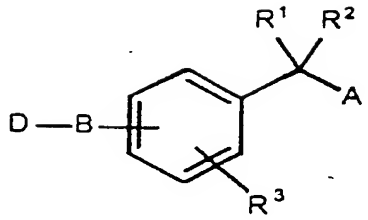
succession, and the mixture is stirred at -78°C under inert atmosphere for 4 h, then it is left to cool and immediately added with water (15 ml) and 1M HCl (15 ml). The mixture is extracted with ethyl ether and dried, the solvent is evaporated off and the residue is purified by flash chromatography on silica gel column eluting with petroleum ether:ethyl ether mixtures of increasing polarity, thereby obtaining 0.722 g of the title compound (50% yield).

5E 2-(4-Isobutyl-2-methoxyphenyl)butanoic acid

Following the process described in example 2 (point B), starting from 2-(4-isobutyl-2-methoxyphenyl)butanonitrile, the title compound is prepared (85% yield).

CLAIMS

1. A compound of formula I,



I

wherein:

- A is a $-COOR^4$, $-SO_3R^4$, $-SO_2NHCOR^4$, $-SO_2NHCOOR^4$, $-SO_2NHCONHR^4$, $-CONHOR^4$, $-CON(OH)R^4$, $-N(OH)CONH_2$, $-N(OH)COR^4$, $-CONHSO_2R^5$ group or a 5-tetrazolyl group;
- B is a single bond or a diradical which represents a (C_1-C_4)-alkyl or alkenyl group, a -CO- group, an oxygen atom, a sulfur atom, a NR^4 group, a $-CON(R^4)-$ group or a $-N(R^4)CO-$ group;
- D is a hydrogen, a (C_1-C_6)-alkyl, alkenyl or alkynyl group, a (C_3-C_7)-cycloalkyl or cycloalkenyl group, all these groups optionally having one or more hydrogen atoms substituted by halogen atoms, hydroxy groups, (C_1-C_4)-alkoxide groups or (C_1-C_4)-alkyl groups;
- R^1 and R^2 are independently hydrogen, (C_1-C_6)-alkyl or (C_3-C_6)-cycloalkyl or, taken together, they form a (C_3-C_6)-cycloalkyl;
- R^3 is hydrogen, fluorine, chlorine, bromine, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxide;
- R^4 is hydrogen, a (C_1-C_4)-alkyl or a phenylakyl group of less than 10 carbon atoms;

- R^5 is the same as R^4 except hydrogen;

provided that the compound of formula I is other than:

3-chloro-4-(2-propenyloxy)benzeneacetic acid;

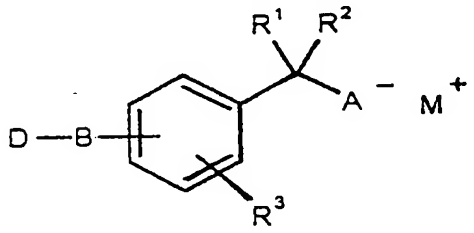
α-methyl-4-[(2-methyl-2-propenyl)amino]benzeneacetic acid;

α-methyl-4-(2-methylpropyl)benzeneacetic acid;

4-(2-methylpropyl)benzeneacetic acid;

and N-hydroxy-α-methyl-4-(2-methylpropyl)benzeneacetamide,

as well as all the possible stereoisomers or mixtures of the compounds of formula I, the pharmaceutically acceptable solvates and salts thereof, in particular the salts represented by the formula Ia,



Ia

wherein:

wherein M^+ is an alkali metal cation (e.g. Na^+, K^+), or the half amount of an alkaline-earth metal cation (e.g. 1/2 Ca^{2+}, 1/2 Mg^{2+}), or it represents a cation derivative of an amine or ammonium quaternary salt (e.g. triethylammonium, tris(hydroxyethyl)methylammonium).

2. A compound according to claim 1 wherein A is a group selected from $-COOR^4$, $-CONHOR^4$, $-CON(OH)R^4$ or $-CONHSO_2R^5$.

3. A compound according to claim 1 wherein A is a group selected from $-SO_3R^4$, $-SO_2NHCOR^4$, $-SO_2NHCOOR^4$ or $-SO_2NHCONHR^4$.

4. A compound according to claim 1 wherein A is a group selected from $-N(OH)CONH_2$ or $-N(OH)COR^4$.

5. A compound according to claim 1 wherein A is a 5-tetrazolyl group.

6. A compound according to any one of claims 1 to 5 selected from the following ones:

5-[1-[4-(isopropylamino)phenyl]ethyl]-1*H*-tetrazol;

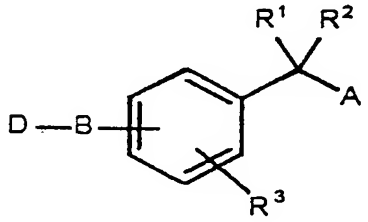
2-[4-(isobutylsulfinyl)phenyl]propionic acid;

2-[2-fluoro-4-(isopropyloxy)phenyl]propionic acid;

2-[3-(cyclopropylmethyl)phenyl]propionic acid;

2-(4-isobutyl-2-methoxyphenyl)butanoic acid;

7. A compound of formula I,



I

wherein:

- A is a $-COOR^4$, $-SO_3R^4$, $-SO_2NHCOR^4$, $-SO_2NHCOOR^4$, $-SO_2NHCONHR^4$, $-CONHOR^4$, $-CON(OH)R^4$, $-N(OH)CONH_2$, $-N(OH)COR^4$, $-CONHSO_2R^5$ group or a 5-tetrazolyl group;
- B is a single bond or a diradical which represents a (C_1-C_4)-alkyl or alkenyl group, a -CO- group, an oxygen atom, a sulfur atom, a NR^4 group, a $-CON(R^4)-$ group or a $-N(R^4)CO-$ group;
- D is a hydrogen, a (C_1-C_6)-alkyl, alkenyl or alkynyl group, a (C_3-C_7)-cycloalkyl or cycloalkenyl group, all these groups optionally having one or more hydrogen atoms substituted by halogen atoms,

hydroxy groups, (C_1-C_4)-alkoxide groups or (C_1-C_4)-alkyl groups;

- R^1 and R^2 are independently hydrogen, (C_1-C_6)-alkyl or (C_3-C_6)-cycloalkyl or, taken together, they form a (C_3-C_6)-cycloalkyl;
- R^3 is hydrogen, fluorine, chlorine, bromine, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxide;
- R^4 is hydrogen, a (C_1-C_4)-alkyl or a phenylakyl group of less than 10 carbon atoms;
- R^5 is the same as R^4 except hydrogen;

provided that the compound of formula I is other than:

3-chloro-4-(2-propenyloxy)benzeneacetic acid;

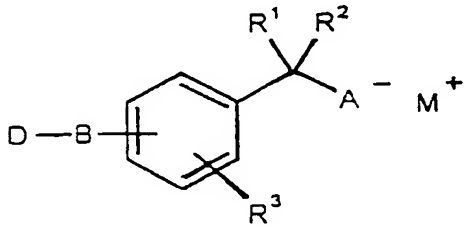
α-methyl-4-[(2-methyl-2-propenyl)amino]benzeneacetic acid;

α-methyl-4-(2-methylpropyl)benzeneacetic acid;

4-(2-methylpropyl)benzeneacetic acid;

and N-hydroxy-α-methyl-4-(2-methylpropyl)benzeneacetamide,

as well as all the possible stereoisomers or mixtures of the compounds of formula I, the pharmaceutically acceptable solvates and salts thereof, in particular the salts represented by the formula Ia,



Ia

wherein:

wherein M^+ is an alkali metal cation (e.g. Na^+, K^+), or the half amount of an alkaline-earth metal cation (e.g.

1/2 Ca^{2+}, 1/2 Mg^{2+}), or it represents a cation derivative of an amine or ammonium quaternary salt (e.g. triethylammonium, tris(hydroxyethyl)methylammonium), for use as selective cyclooxygenase-I inhibitors.

8. The use of a compound as claimed in any one of claims 1 to 6 for the preparation of a medicament for the treatment of inflammatory or allergic origin, as well as for the treatment of pain or fever, in patients with pre-existent ulcers or gastrointestinal disorders or with relapses of gastric lesions, gastric bleeding and coagulation problems.

9. The use according to claim 8 wherein the diseases of inflammatory or allergic type are: allergic rhinitis, allergic conjunctivitis, rheumatoid arthritis, osteoarthritis, tendinitis, bursitis or psoriasis.

10. The use according to claim 8 wherein pain or fever are symptoms associated with rheumatic fever, lumbar and cervical pains, viral infections, dysmenorrhea, headache or toothache, myositis, neuralgia, synovitis, arthritis including osteoarthritis and rheumatoid arthritis, ankylosing spondylitis, bursitis and burns.

11. The use according to claim 8 wherein the gastrointestinal disorders pre-existent to the treatment are: peptic ulcers, gastrointestinal ulcers, intestinal inflammatory diseases, Crohn's disease or ulcerative colitis, gastritis, local enteritis and diverticulitis.

12. The use according to any one of claims 8 to 11 in those cases in which conventional NSAIDs are contra-indicated, in patients with peptic ulcers, gastrointestinal ulcers, intestinal inflammatory diseases, Crohn's disease or ulcerative colitis,

gastritis, local enteritis and diverticulitis, or with relapses of gastric lesions, gastric bleeding and coagulation problems.